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JANUARY 1947

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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1847—CENTENNIAL OF THE ACADEMY—1947

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THE NEW YORK ACADEMY
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CENTENNIAL CELEBRATION

1847 – 1947

THE year 1947 marks the completion of the first hundred years of The New York Academy of Medicine. As is fitting and proper, the Council and Trustees of the Academy have decided to devote the months of March and April 1947 to a celebration of this Centenary.

The dominant thought which will motivate the program of this Celebration will be, not so much the recital of the Academy's fascinatingly interesting history, as an evaluation of its accomplishments in terms of present day thought and its implications for the future of medicine and the community at large. For a century, the Academy has served the medical profession—practicing, teaching, and fostering research in matters of medical education, public health and public relations. From these roots have grown its work for the public weal, particularly in public health and welfare. The Academy has become a valued portion of the warp and woof of our whole community fabric. This foundation of a hundred years is important only in so far as it serves as a basis for future intellectual and spiritual growth; only in so far as it prepares the Academy to meet new problems and to explore new fields.

This Centennial Celebration will open with a Dinner on March 6,

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1947 at the Waldorf-Astoria Hotel, to which the Fellows, their wives and friends of the Academy will be invited.

Subsequent to the Dinner, extending over the span of two months, each of the eleven Sections of the Academy will present programs in keeping with the spirit of the Centenary. These programs are under the charge of the Section Chairmen. It is the hope of the Centennial Committee that through these media, the entire Fellowship of the Academy may participate actively in this Centennial Celebration.

In addition to the Section meetings, there will be four conferences or Institutes—one on Public Health; another on the problems of Medical Education; a third devoted to what is termed Social Medicine, a discussion of the influence of modern medicine on the larger social groups, as well as conversely, the implications of the impact of changing social orders on medicine itself. The fourth Institute will consider the problems of specialized libraries, particularly medical and scientific libraries. These Institutes will occupy periods of two to three days each.

Societies and organizations affiliated with the Academy either in fact, or through association of interests and aims, will coöperate in the Centenary.

Two publications will appear in 1947 under the auspices of the Academy, which will be of major interest. The Report of the Committee on Medicine and the Changing Order will be published by the Commonwealth Fund prior to the initiation of the Centennial Celebration. This work represents the results of a three and a half year study on the part of a large Committee of Fellows of the Academy and laymen. Later in the year, there will appear a History of the Academy over its first century. This volume has been in the process of preparation for about two years and promises to be a major contribution, not only to the history of medicine in New York, but as well a contribution to the history of the City itself.

Inherent in the aims of these plans is the thought of having as broad a participation as possible by the entire Fellowship of the Academy in the Centennial Celebration. Details of programs and dates of various exercises will appear in the Academy Bulletin, and in addition, will be sent to each Fellow individually.

TUMORS OF THE THYROID*

SHIELDS WARREN

Pathologist, New England Deaconess Hospital, Boston

THYROID tumors have been of constant interest because of the difficulty of diagnosis of certain types; now the possibility has been raised that radioactive iodine may offer a useful therapeutic tool.

Most enlargements of the thyroid are not tumors. Enlargement of the gland, either diffuse or nodular, is much more frequently due to metabolic disorders than to neoplasia. Until recent years, there has been much confusion between the true adenomas of the thyroid and the nodular hyperplasias, and still some room for argument exists.

I have found the following criteria for adenoma of the thyroid to be helpful in differentiating this lesion from thyroid nodules of non-neoplastic origin. First, an adenoma should represent a single homogeneous type of tissue. Second, it should be definitely encapsulated. Third, it should compress surrounding thyroid tissue. Usually, it differs sharply in histology from the surrounding tissue. In some of the nodular goiters, even these criteria may prove unsatisfactory and uncertainty may exist as to type of lesion with which we are dealing.

The origin of thyroid adenomas is as uncertain as the origin of adenomas in other organs. In our laboratory five types of adenoma are recognized: the embryonal adenoma, in which masses and strands of poorly differentiated thyroid cells traverse a rather gelatinous stroma; the fetal adenoma, in which poorly developed follicles occur, usually embedded in a rather abundant gelatinous stroma; the simple adenoma which may closely resemble the histologic picture of the normal thyroid gland; the colloid adenoma, in which extensive storage of colloid occurs, and the follicles are greatly distended; the Hürthle cell type of adenoma, characterized by large polyhedral cells with rather strikingly clear cytoplasm.

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* Read at The New York Academy of Medicine at the 19th Graduate Fortnight, October 8, 1946.

The so-called toxic adenoma is quite frequently diagnosed but very rarely occurs. Usually, when this term is applied, it is used to describe a nodular goiter with associated hyperthyroidism. Hyperfunction of the cells of an adenoma is one of the rarest changes encountered.

The adenomas are also of special interest because of the borderline position which they occupy between the benign tumors on the one hand and the malignant tumors on the other. There is a group of thyroid adenomas, usually indistinguishable from other adenomas grossly, which give rise to metastasis. The metastases may faithfully reproduce the parent adenoma or they may be even more differentiated resembling well-formed adult thyroid tissue, the so-called benign metastasizing goiter. The only clue to the malignancy of these tumors may be invasion of one or more veins by the neoplastic tissue. Sometimes this is grossly obvious with a solid cord of tumor filling one of the major thyroid veins or even the jugular vein. More often it is relatively inconspicuous and only microscopic examination will reveal its presence. This vascular invasion may or may not be accompanied by some invasion of the capsule. Not every case that shows microscopic evidence of blood vessel invasion develops metastases. Indeed, the frequency is under 10 per cent. It is likely that a relatively extensive amount of vascular invasion occurs before metastases become established, since the proportion of tissue removed for histologic examination is relatively small. Interestingly enough, I have seen only one case in which we did not find blood vessel invasion and in which metastases subsequently developed.

As would be expected from the high degree of differentiation of these tumors, their clinical course is relatively slow. Metastases occur most frequently in bone. In one case I recall, the patient lived seven years after the metastases were discovered. Likewise, a long latent period may pass between the development of the primary tumor and the appearance of metastases.

The commonest of the adenomas to show blood vessel invasion, as would be expected from their growth potentialities, are the embryonal and the fetal adenomas. In checking for the occurrence of blood vessel invasion, it is important not to be misled by artefacts. In the course of preparation of the sections, it is quite possible that portions of the tumor may be dislodged and caught in the blood vascular spaces. Consequently, I always like to see actual invasion of the wall of the vessel by the

tumor or adherence of the tumor tissue to the wall.

As was so clearly pointed out by Graham, the propensity to invade blood vessels is quite striking in all types of thyroid malignant tumors, regardless of their degree of differentiation, and is consequently a very valuable criterion of malignancy.

There has been a good deal of controversy concerning the papilliferous tumors. These may arise from the thyroid proper or from lateral aberrant thyroid tissue. The five types described by Moritz and Bayless are useful in considering this group: (1) The papilliferous cystadenoma, a benign tumor which represents hyperplasia of the lining epithelium of a cystic adenoma; (2) the papilliferous adenoma, which represents epithelial proliferation of an hyperplastic type within the follicles of a pre-existing adenoma, and is non-malignant; (3) the papilliferous carcinoid, which represents focal papillary hyperplasia, is non-encapsulated and occurs in a non-neoplastic thyroid gland; (4) the papilliferous adenocarcinoma arising from malignant change in a papilliferous cystadenoma, which shows capsular invasion or metastasis to regional lymph nodes; and (5) the papilliferous malignant adenoma, which shows a papillary intra-acinar hyperplasia in an adenoma with malignant characteristics, i.e., blood vessel invasion, capsular invasion, and sometimes metastasis to regional lymph nodes.

It has been our custom to differentiate three types of true papillary tumors: The benign papillary cystadenomas which may originate either within the thyroid or in lateral aberrant thyroid tissue, which are not clinically dangerous; the malignant papillary adenocystomas which seem to have the same origin as the foregoing but which, because of a greater growth potential, may metastasize chiefly to regional lymph nodes or lungs, invade blood vessels, and invade local tissues; the papillary adenocarcinoma which will be mentioned further later.

Even in those papillary cystadenomas that are malignant, the clinical course tends to be relatively slow, and fortunately, the results obtained with surgery combined with roentgen radiation are fairly satisfactory. Two-thirds of all patients treated were surviving at the end of five years.

When one finds a papillary tumor of thyroid origin in the neck, the problem always arises as to whether or not the thyroid should be removed either wholly or in part. If the thyroid is normal on palpation, there is no reason for operative interference, and it may safely be assumed that the tumor is of lateral aberrant origin. If, however, there is

enlargement or irregularity of the thyroid, at least a hemi-thyroidectomy including the abnormal tissue is indicated.

In the group of thyroid tumors of moderate malignancy we include the adenocarcinomas. These may be papillary, of alveolar type or of Hürthle cell type. They often give indication of origin from pre-existing adenomas, although not infrequently the development of the tumor has destroyed all evidence of the initial focus and the existence of a pre-existing adenoma may be deduced only from the history given by the patient.

The first subgroup of adenocarcinomas is the papillary form. This frequently invades the thyroid gland and adjacent normal tissue. The epithelium is variable in size and shape, usually with fairly well-defined cell borders. The epithelium tends to heap up rather than to form a single well-defined layer as is the case in the papillary cystadenoma. Occasionally, follicles and colloid may be present in the tumor. About 80 per cent of the patients bearing these tumors survive five years.

The alveolar type of adenocarcinoma is less differentiated and is made up of masses and strands of epithelial cells. The stroma is variable in amount. Here and there definite follicles are formed. These rarely may contain colloid. In this group only 27 per cent survived five years.

The rarest of the adenocarcinomas is the Hürthle cell type, which resembles closely the Hürthle cell adenoma already described, with large, clear acidophilic cells, but the arrangement is irregular, and invasion of adjacent thyroid tissue occurs. Mitoses, while not abundant, occur occasionally. The highly malignant carcinomas of Group 3 vary widely in appearance. The undifferentiated carcinoma simplex or small cell carcinoma occurs in two distinct forms; the compact form is readily recognizable by its masses of anaplastic epithelial cells without formation of follicles or of lumina. There is usually a high degree of mitotic activity. The diffuse type is much more difficult to recognize and is frequently confused with lymphoma or even chronic thyroiditis. The cells of the tumor are widely scattered. They are small with scanty cytoplasm and a rather small pyknotic nucleus. The stroma is rather dense, and the cells of the tumor are irregularly scattered through it, replacing much of the normal thyroid structure and extending out into the surrounding tissues. To render the picture more confusing, there may be scattered lymphocytes and macrophages present in the stroma as well. Fortunately, there are usually some small clusters of the cells

arranged in characteristic epithelial pattern. In this group only 22 per cent survived.

The giant cell carcinoma, sometimes called carcinosarcoma, is the most striking of the thyroid malignant tumors. Its large, bizarre cells and irregular mitoses make it easily recognized upon microscopic examination. It tends to occur in women about 50 or 60 years of age. It is very rapidly growing, extending widely and not infrequently compressing the trachea. The texture of the tumor is soft and meaty, rather more suggestive of a sarcoma than of a carcinoma.

In addition to these more frequent carcinomas of the thyroid, there are three malignant tumors which occur there very rarely. First, the true fibrosarcoma which may be recognized by the fact that its cells form fibroglia and collagen fibrils. Second, epidermoid carcinomas occasionally develop, either from epithelial nests or by metaplasia of thyroid epithelium. The third type is a true lymphoma of the thyroid, which must be differentiated from both the struma lymphomatosum of Hashimoto and the carcinoma simplex of diffuse type. Its appearance and behavior is comparable to that of lymphomas occurring elsewhere.

TUMORS OF THE FEMALE GENITAL TRACT*

RICHARD W. TE LINDE

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I WAS asked by the Committee on Medical Education to make my remarks of a practical nature since most of you in the audience are engaged in the practice of general medicine. To this I gladly acceded. The general practitioner still represents the backbone of the American medical profession and by his excellence or mediocrity our present system of medical care stands or falls. Meetings such as these held during this fortnight are essential to keep the men who first see the patient abreast of progress in the various medical specialties. If I can add just a little to your practical knowledge in the field of genital tumors, I will feel well repaid for my efforts.

The female genital tract is particularly prone to the development of a variety of neoplasms. Consider the variety of tissues in the genital tract. The vulva, the vagina and the vaginal portion of the cervix are covered with stratified squamous epithelium. The cervical canal, the uterine cavity and the tube are lined with columnar epithelium. The ovary is covered with a special epithelium known as germinal epithelium. Within the ovaries are embryonic epithelial nests, the granulosa cells of the follicles, the lutein cells and, finally, the totipotential cells within the follicles, the ova. All of these organs also have mesodermic tissue, fibrous tissue and muscle from which benign and malignant connective tissue tumors may arise. Consider also that these tissues are frequently subjected to the irritation of inflammation and that they are constantly subjected to the influence of the hormones. There is constant activity during the monthly cycle in the ovaries, tubes and uterus of the sexually mature woman. During pregnancy there is an overwhelming hormonal stimulation which causes growth and alterations of all the pelvic tissues. There is, then, little wonder that the limits of physiological growth are often exceeded and pathological growths develop.

* Given October 14, 1946 at the 19th Graduate Fortnight of The New York Academy of Medicine.

In making a rapid survey of the female genital tract I shall start at the vulva and progress upward. The vulva is occasionally the site of benign growths, such as lipomas and fibromas. Rarely, they become so large that they interfere with sitting, walking and coitus and removal becomes necessary. Cancer of the vulva is more commonly encountered than these large benign tumors but still must be classified as a rare tumor. It represents about 3 per cent of genital malignancies. It usually appears as a small lump or ulcer which often requires biopsy to establish the diagnosis. If properly treated with radical vulvectomy and radical resection of the inguinal and femoral glands the five year salvage rate is as high as 58 per cent. Irradiation therapy is much less satisfactory and the post-irradiation burning sensation of the vulva may make the victim extremely uncomfortable.

Perhaps the most important point for us to remember about carcinoma of the vulva is that it is to some degree a preventable disease. In approximately half the cases of vulval carcinoma, it is preceded by leukoplakia. The symptom of leukoplakia is itching and every case of pruritus vulvae should be carefully examined for leukoplakic changes in the skin. When found, the area should be excised, even though it involves the entire vulva. The precancerous nature of leukoplakia has been proven beyond doubt. I have observed two patients with leukoplakia of the vulva who were not operated upon for good medical contraindications and who developed cancer directly under observation. Approaching it from a pathological angle, Smith and Graves found that in 21 vulvas removed for cancer, leukoplakia was found elsewhere in the vulva in 16 cases.

The vagina is too rarely the site of neoplasm to warrant much consideration here. Fibromas and papillomas are occasionally seen and equally rare is carcinoma. The latter is almost uniformly fatal. It cannot be successfully treated surgically. If sufficient irradiation is used to give reasonable hope for a cure, rectovaginal or vesicovaginal fistula will almost certainly develop.

The cervix is the point in the generative tract most susceptible to carcinoma. Benign polyps are also common. The incidence of malignancy in them is extremely low but when removed they should be sectioned to exclude microscopic cancer. Although the chance of malignant change occurring secondarily in a benign polyp is extremely small, occasionally endocervical cancer protrudes from the external os

and looks not unlike a benign polyp. The real importance of polyps lies in the fact that their initial symptom is usually intermenstrual spotting which is indistinguishable from that of cervical carcinoma. Whenever it occurs, speculum examination and cervical biopsy are indicated.

It seems that it should be an extremely simple matter to teach the medical profession that every woman over thirty with intermenstrual bleeding should be subjected to a speculum examination and cervical biopsy. And yet, these simple procedures are neglected every day. I now have under treatment a woman with cervical cancer who had seen three practitioners who refused, even at her insistence, to make a cervical biopsy. Such experiences are discouraging from the standpoint of education of the medical profession but they do indicate that much can be accomplished by direct education of women. The statistics of Norman Miller from the University of Michigan have made a great impression on me and I would that practitioners who see the patients first would be equally impressed. Miller found in a series of uterine cancers that an average of seven months elapsed between the appearance of the first symptom of cancer and the time the patient saw her family physician. That loss of time is the fault of the patient and perhaps it can be corrected by education of the public. But, four more months elapsed between the time the patient saw her family doctor and the time when she got under the care of one who was in a position to institute proper therapy. Thus a total of eleven months were lost and this loss of time usually spells the difference between success and failure in cancer.

I wish to say a few words about a phase of this subject in which I am especially interested. I refer to the early microscopic diagnosis of biopsy specimens. Since we are in a large measure ignorant of the cause of cancer and have no specific therapy for advanced cancer, it seemed to us that perhaps the greatest contribution that could be made within the bounds of the present state of our knowledge of these fundamentals would be along the line of early diagnosis. Accordingly, we have been making a vast number of biopsies of normal and abnormal cervices, many of which were scheduled to be removed in the course of hysterectomies for fibroids. We believe it is now possible to diagnose cervical cancer in the preinvasive stage. We have found in the vast majority of the cases in which preinvasive cancer was found in the biopsy, that early invasive cancer can be found if the entire removed cervix is cut into blocks and many sections made. We have been impressed also with the

number of these cases in which, on careful questioning, slight intermenstrual bleeding was noted, especially after coitus. I am sure that most of you are not interested in the finer points of gynecological pathology but it is important for you to know that there are laboratories to which you can send your biopsies and which will give you an intelligent diagnosis. I do not mean that you can get an expert opinion from every general pathologist but there are laboratories in this city where specially trained gynecological pathologists can do this for you.

It is our belief that cancer of the cervix may remain in this precancerous stage for months and even years before becoming invasive. If this is true, we have a recognizable cervical lesion which can be discovered in ample time to be cured. We base our belief in the long existence of cancer in the preinvasive stage on at least two facts. The average age of the women in our series was 36 years, whereas the average age of cancer of the uterus in general is 48 years. Furthermore, in two cases of advanced cervical cancer we discovered that we had in our laboratory previous biopsies. On reviewing the earlier sections we found the typical intra-epithelial lesions. In one instance the biopsy had been done 3½ years before and in the other 8½ years. At the Womens Free Hospital in Brookline the experience has been identical to ours. Among their cases of advanced cervical cancer they found four that had had biopsies years before which showed the typical intra-epithelial lesions. Incidentally, this experience of Smith's and ours gives strong support to the view that these early lesions are actually cancer, a point about which some doubt has been cast by some pathologists.

It has been our practice in the past six years to treat these cases of microscopic cancer by radical total hysterectomy. The operation which we do includes the removal of a liberal cuff of vagina with the cervix, but does not include lymph gland resection as in the typical Wertheim operation. We have chosen hysterectomy rather than irradiation for two reasons. Many of these cases occur in women in the third decade of life and we have chosen to save an ovary in some of them. Since the ovary is a late site of cervical cancer metastasis we have felt safe in doing this and our results have not caused us to regret it. In addition, we wished to check our diagnoses by cutting the entire cervices into blocks for histological examination. At the time of our last check up three years ago all of the patients were well up to four years. We are now in the process of following up a much larger series.

I do not wish to convey the impression that our routine treatment of cervical carcinoma is panhysterectomy. We employ it only for these microscopic lesions. In general, radium to the cervix and deep x-ray to the pelvis have proven far superior to surgery in the treatment of cervical cancer. The five year salvage rate in the better clinics is in the neighborhood of 25 per cent.

However, there is an experiment being carried out now in the clinic of Dr. Joe Meigs at the Massachusetts General Hospital which should be watched by all of us with the greatest of interest because it is possible that the outcome of this experiment may change our present ideas. Meigs felt that the radical Wertheim panhysterectomy, which formerly carried a mortality of about 12 per cent, should be re-evaluated in the light of modern surgical measures, such as the frequent use of blood transfusion, plasma and fluids. Accordingly, he has performed the radical Wertheim operation on approximately 100 women with relatively early cervical cancer without a single death. It is too early to evaluate the five year salvage but Meigs has at least shown that the Wertheim operation is a relatively safe procedure today when modern precautions are taken. While we are awaiting the final answer from Meigs on five year salvage, I cannot condemn too strongly the rather common practice of many general surgeons of performing an ordinary panhysterectomy for this disease. The salvage from this practice is practically nil and Meigs' experiment is in no way intended to encourage these surgeons.

On progressing to the corpus uteri, let us first consider the commonest of all pelvic tumors, myomata. They are so common that it would seem that their correct treatment would be universally known and practiced. Yet, that does not seem to be case. If I were asked to offer a criticism of the present day treatment of myomata, I would say that too many of them are operated upon without justification. I could not select a better group before which to make this statement than one composed largely of practitioners for, after surgery has been advised by the surgeon, the patient often goes back to her friend, the family doctor, for her final advice. Recently I saw a woman with asymptomatic fibroids who had been advised by three prominent surgeons in a middle western city to have a hysterectomy. She returned to her practitioner for the final word. He told her that inasmuch as fibroids were benign tumors and since she was free from symptoms he could see no indication

for surgery. He sent the patient to me for another opinion. I thought that the family physician was quite right and the woman was spared a useless operation.

In general, asymptomatic fibroids require no treatment except insofar as they may be a factor in future childbearing. The corollary to this statement is that the older a woman is, the less likely will treatment be necessary. When future pregnancy is planned, however, the problem of the asymptomatic fibroid is one which requires the best of obstetrical and gynecological judgment. One must consider the probable effect of the tumor on conception and on the course of pregnancy and on delivery. One must weigh carefully the dangers of proceeding with a pregnancy in the presence of the tumors and the advantages and disadvantages of myomectomy, remembering always that a planned myomectomy may eventuate in a hysterectomy. If the myomatous uterus is already the site of pregnancy one must consider the possibility of an abortion, which may be quite complicated in a myomatous uterus. Also to be considered are the interference of the tumor with the birth of the child and the advantages of Cesarean section at term, with or without hysterectomy.

Aside from the relation to pregnancy, the indications for treatment are simply stated. Excessive bleeding, usually of the menorrhagic type, abdominal discomfort from pressure and distortion of the abdomen by the presence of a large tumor are the usual symptoms which necessitate treatment. Except when there is evidence of postmenopausal growth, the possibility of malignancy is seldom an indication for hysterectomy. The incidence of malignant change in the tumor is less than one per cent and the patient runs an equal risk from hysterectomy.

The symptom of bleeding from fibroids is worthy of a short analysis. It may be stated at the outset that the presence of blood coming from a fibroid uterus does not justify the assumption that the fibroid is responsible for the bleeding. This is true even when the bleeding is confined to the menstrual period. Multiple pathological lesions in the uterus are common and the fibroids may be quite incidental. When the abnormal bleeding is of the intermenstrual type, the chances are strongly in favor of the bleeding being due to a lesion other than the fibroids. It is a rule on our service to biopsy the cervices of all women upon whom a hysterectomy for fibroids is contemplated when there is a history of intermenstrual spotting. We do this regardless of the innocent

appearance of the cervix. It has been surprising how many early cervical cancers we have uncovered in this way.

When postmenstrual bleeding occurs in the presence of a fibroid uterus, one should never assume that the fibroid is the cause of the bleeding. The chances are great that some other lesion is responsible for the bleeding and that lesion is very apt to be malignant. The next logical question is whether a fibroid can ever be responsible for postmenopausal bleeding. The answer is: Yes, but rarely. We have observed asymptomatic intramural fibroids at the time of the menopause work their way into the uterine cavity and cause even profuse bleeding after the menopause, making a hysterectomy necessary.

Carcinoma of the corpus uteri is only about one-eighth as frequent in occurrence as cervical cancer. It occurs, on an average, a decade later in life but in spite of being primarily a postmenopausal disease, it occasionally occurs in young women. We have seen a few cases in the fourth decade of life and our youngest case was in a Negress of twenty-two. I mention these occasional early occurrences only to remind you that intermenstrual bleeding can mean malignancy at almost any age. The diagnosis can only be made with certainty by curettage although one must strongly suspect it in bleeding postmenopausal women when the cervix looks normal.

Most everyone agrees today that the treatment of corpus malignancy should be some form of irradiation followed by total hysterectomy and double salpingo-oophorectomy. There is some difference of opinion as to whether irradiation should be given by x-ray or by intrauterine application of radium. It is probable that there is not much choice, but it should be remembered that, regardless of how irradiation is given, a large percentage of the irradiated uteri will show active cancer in the uterine cavity. Statistical studies have pretty well shown that irradiation plus surgery is better than surgery alone or irradiation alone. However, many of these carcinomas occur in very old women who are poor surgical risks and it is comforting to know that something can be accomplished by irradiation alone. The five year salvage from irradiation is in the neighborhood of 35 per cent which is about half that of irradiation followed by surgery.

The problem of ovarian neoplasm is comparable to that of tumors of the breast. Ovarian tumors, like breast tumors, are often silent growers and their removal is necessary before a verdict can be given regarding

malignancy. The incidence of malignancy in ovarian growths is so high that one cannot afford to take a chance on their benign nature. Furthermore, clinical experience, coupled with pathological studies, has demonstrated that ovarian tumors may be benign for years and finally become malignant. Consider, for example, the large ovarian tumor that has been responsible for noticeable abdominal enlargement for years. Suddenly, there is a rapid increase in size of the abdomen. The tumor is removed and on pathological examination it is found to consist chiefly of benign cystadenoma with areas of unmistakable carcinoma. A case such as this demonstrates that the history of long duration by no means rules out malignancy. Besides the danger of malignancy there are other potentialities which endanger life and increase operative risk. The commonest of these are torsion of the pedicle, infection and rupture.

The value of the admonition that all ovarian neoplasms should be operated upon depends on the ability of the examiner to distinguish between ovarian enlargement due to neoplasm and enlargement due to other causes. Slight enlargements, due to multiple small follicular cysts or single follicular or corpus luteum retention cysts, are common. To distinguish them from small neoplastic ovarian enlargements is not always easy, but it is important because of the possibility of malignancy, present or future, in all neoplasms of the ovary. Retention cysts often disappear spontaneously and their immediate removal would subject the patient in many instances to useless laparotomy. Multiple cystic retrogressing follicles may increase the ovary to two or three times the normal size. Such ovaries usually feel semisolid, and the surface is slightly nodular due to multiple small cysts. Single retention cysts are usually thin walled, often easily compressible, but at times they are tense. A thick-walled cyst is more apt to be neoplastic. Tumors that feel cystic in some areas and solid in others are liable to be malignant. A solid or cystic tumor with a nodular, irregular contour is frequently malignant. The solid smooth-surfaced tumor may be malignant, but may also be a fibroma. In spite of the greatest tactile skill, there are occasions when doubt will exist as to whether an ovarian enlargement is due to a retention cyst or a neoplastic cyst. Such cases should be watched at monthly intervals. Retention cysts may persist or disappear; the true neoplasm usually can be detected due to increase in size. The palpation of irregularities on the surface of the tumor is cause for suspecting papillary outgrowths that indicate neoplasm, and one should bear in mind that

all papillary tumors are potentially malignant. When one becomes reasonably certain that one is dealing with a neoplasm, a laparotomy should be done. When considerable doubt exists the decision may be made by direct visualization of the tumor through the culdescope.

Because ovarian neoplasms often grow silently, it is common to have the patient present herself for examination with signs of advanced ovarian malignancy. The silent growth of ovarian neoplasms constitutes one of the greatest reasons for periodic routine pelvic examinations. Abdominal pain or abdominal enlargement is the symptom that frequently brings the patient to the physician. These symptoms often mean spreading of the neoplasm beyond the ovaries with peritoneal implants and ascites. Pemberton found that 36 per cent of the ovarian carcinomata were inoperable when first seen. The question of laparotomy, when there is obvious advanced ovarian cancer, should usually be answered in the affirmative. When the patient's condition is very poor, peritoneoscopy with biopsy to confirm the diagnosis may suffice, but when the patient's general condition warrants it, she should be given the benefit of a laparotomy. Not infrequently a seemingly inoperable growth may be removed completely or nearly completely, and the patient remain well for years. The cure of a patient by incomplete removal of a malignant growth seems contrary to the usual principles of surgery and pathology, but we have observed cure even without postoperative irradiation. Furthermore, there is a group of papillary ovarian tumors that implants small papillary growths in a widespread manner over the peritoneum. These tumors are associated with marked ascites. Before operation, and even at the operation, they cannot be distinguished with certainty from truly malignant tumors, and yet after a complete pelvic operation with removal of the parent tumor, the implants retrogress and the patient remains permanently well. To refuse surgery in such a case, on the grounds that the ascites indicates inoperability, might withhold from the patient the chance of a permanent cure.

Benign unilateral ovarian neoplasms may be cured by unilateral oophorectomy, and this is the proper therapy in young individuals provided the opposite ovary appears to be normal. The tendency of certain types of benign ovarian tumors to bilaterality is well known. Suffice it to say here that the opposite ovary should be carefully examined for evidence of a small growth. In case of doubt, a biopsy and frozen section may be advisable. In menstruating women of forty or over the

preservation of the opposite ovary, although desirable, is not as essential as in younger women, and one might remove the opposite ovary on less evidence than would be required in a younger individual. It is a good rule to have an assistant in the operating room open every apparently benign ovarian cyst after removal. If intracystic papillomas are found with an appearance at all suggestive of malignancy, a frozen section should be made, especially in younger women in whom the preservation of the remaining ovary is very desirable. After the menopause, it is our custom to remove the opposite tube, the ovary and the uterus even though the unilateral tumor is benign, provided the patient's condition does not contraindicate the necessary added surgery.

When the ovarian neoplasm is obviously malignant, a hysterectomy and a double salpingo-oophorectomy are done routinely. The importance of removal of both ovaries in all cases is emphasized by the findings of Norris and Murphy. These investigators discovered that when one ovary was grossly malignant at operation and the other grossly benign, in 17.5 per cent the benign-appearing ovary proved to be malignant when examined histologically. A total hysterectomy is preferred to subtotal, but in some instances, when the tumors are fixed and the operation difficult, it is wise to do the lesser operation, rather than increase the operative risk by removing the cervix.

Most ovarian tumors are resistant to x-ray therapy; it never should be employed as a substitute for surgery. When a tumor is completely inoperable, x-ray may be resorted to, although the results are almost always disappointing. Very rarely, however, does one see a far-advanced or recurrent ovarian neoplasm melt away under ray therapy and the patient remain well for many years. The value of postoperative irradiation is still debatable. The literature is contradictory, with the weight of evidence slightly in favor of postoperative irradiation. It is our custom to irradiate postoperatively those cases in which there is obvious carcinomatous tissue left at operation, as well as those cases in which there is some question as to the completeness of the operation. We do not feel that statistical results justify the routine postoperative use of x-ray in those cases in which there is every evidence of a clean and complete surgical removal; nor do we irradiate those patients in whom massive carcinoma has been left at operation and whose general condition is very poor.

TUMORS OF THE BREAST*

GRANTLEY WALDER TAYLOR

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CARCINOMA of the breast is the commonest type of serious malignant disease in the female. Tumors of the breast are important to consider only for two reasons: first, the fact that they may be confused with carcinoma; second, that they may be precancerous conditions. Although these are the chief reasons for discussion of the other types of breast tumor, there are certain features of interest in many breast tumors which merit consideration.

In the breast, as elsewhere in the skin and subcutaneous tissues, there may occur a variety of benign and malignant tumors which are not essentially mammary in origin. Thus, there may be neoplasms of the skin, and also such benign tumors as lipoma, fibroma, hemangioma, and the like. These are of importance only in so far as they may be confused with intrinsic mammary tumors; and in the fact that they may participate in the extraordinary physiological changes which involve the breast itself during pregnancy and lactation. One illustrative case may suffice; an extensive cavernous hemangioma of the breast in which arteriovenous communications developed during pregnancy, resulting in a rapid increase in size, a bruit and thrill; and seriously threatening the cardiovascular equilibrium.

In consideration of benign conditions peculiar to the breast, mention must be made of supernumerary breasts, and islands of breast tissue. These are commoner than is usually supposed. They may manifest themselves for the first time during pregnancy or lactation, as painful swellings in the axilla, or along the border of the pectoral muscle. Sometimes they overlap the breast itself, and appear as a separate lobulation of tissue near the lower border, or more rarely the upper outer border of the normal breast tissue. These islands of supernumerary breast tissue may become carcinomatous, and probably do so as readily as do normal breasts. They may account for some of the instances of apparently

* Given October 14, 1946 at the 19th Graduate Fortnight of The New York Academy of Medicine.

primary breast carcinoma in the axilla without evident involvement of the breast itself. Galactocele, a large solitary cystic mass noted during or following lactation, is rarely encountered although it is described in all textbooks dealing with the breast. It is possible that the cyst represents the ultimate evolution of an isolated and frustrated island of supernumerary mammary tissue.

Adenofibroma, sometimes called fibroadenoma, occurs as a rounded or oval, freely movable encapsulated tumor in the breast of young women as a rule. Histologically it appears to be made up of adenomatous acinar or duct elements with an abundant and dense fibrous stroma. These tumors are usually single, but may be multiple, and appear in both breasts. They are usually about one or two centimeters in greatest dimension when first observed but they grow significantly during pregnancy and lactation. They are most commonly found in underdeveloped small breasts. This fact may be due to some developmental or hormonal reason, or merely due to the fact that they are harder to find, and hence more easily overlooked, in larger breasts. A minor mystery surrounds their fate if they are not removed early. Certainly large tumors of this sort are rare; and the finding of such tumors in older women is most unusual. Rarely, a calcified tumor in older breasts may be interpreted as the end stage of adenofibroma; but it is at least a tenable conjecture that the tumors may regress in later life. It has been suggested that these tumors may become malignant, and develop as sarcoma. However, since sarcoma is a very rare tumor of the breast, and adenofibroma is relatively common, this possibility does not appear to be very likely. A disseminated and non-encapsulated form of this disease, termed adenofibrosis, is now described, and distinguished from the group of generalized breast abnormalities formerly considered together as chronic cystic mastitis. Fibroadenomas, and especially adenofibrosis, may result in symptoms in relation to the menstrual cycle; especially in tenderness and transitory increase in prominence during the premenstrual stage, but as a rule the tumors are symptomless. Excision is usually desirable to establish the diagnosis and it is all that is necessary for treatment although the possible development of similar tumors in the same or other breast warrants follow-up observations.

Nodularity of the breasts, usually symmetrical, most pronounced in the upper outer quadrants and commonly associated with discomfort and engorgement during the premenstruum, is a functional disorder,

presumably related to hormonal disturbance, and important only in exciting apprehension in the patient, and sometimes giving rise to symptoms severe enough in themselves to require an attempt at relief. Unfortunately, attempts at therapy through administration of hormones are not often successful.

Another condition of the breast probably closely related to the hormones, is so-called chronic cystic mastitis. Numerous names have been proposed for the condition; and it is obvious that several different processes are described under this general designation. Cyst formation varies greatly, from multiple minute cysts to one or a few large ones; and there is every degree of epithelial activity from virtual atrophy to a high degree of active hyperplasia. Sometimes there is a relation of manifestations or symptoms to the menstrual cycle, but more often there is no definite relationship. Warren studied the late results in patients in whom this condition had been discovered in partial excisions of breast tissue, and concluded that the incidence of cancer in these patients in later life far exceeded the normal expectancy. He concluded that the condition is definitely precancerous. However, the likelihood of the development of cancer is not so great as to warrant the general recommendation of bilateral simple mastectomy as a prophylactic procedure in these cases. A reasonable program consists in careful surveillance, with exploration at any time that particular masses appear to be open to suspicion.

Intraductal papilloma is a condition first indicated and suspected by the occurrence of a bloody discharge from the nipple. On palpation, often a dilated duct can be felt beneath the edge of the areola. There has been some dispute as to whether these intraductal papillomas are precancerous lesions. Certainly, some carcinomas of the breast originate in this fashion, and it is a problem for the pathologist to decide which of the tumors are benign, which precancerous, and which represent early intraductal carcinoma. The condition is usually multiple and diffuse; and the only certain prophylactic against cancer would be bilateral mastectomy. Alternatively, a policy of frequent observations may suffice to detect carcinoma at an early stage, if it should develop.

Papillary cystadenoma is a similar process, probably involving the acinar rather than duct epithelium, and occurring in the more peripheral parts of the breast. These tumors are more often single, and may attain some considerable size before they are detected. They do not communi-

cate with the ducts, and hence do not present any discharge. They can be definitely regarded as precancerous, and breasts from which they have been excised should be kept under careful observation postoperatively.

Sarcoma of the breast is a relatively rare tumor, in general behaving as fibrosarcoma, although several histological types are described. Our experience with these tumors at the Pondville Hospital was summarized by Rogers and Flo. Surgical removal of the entire breast and fascia of the pectoral muscle is considered sufficient in most cases, although axillary metastasis has occurred in some types of the disease. Inadequate operations invite local and refractory recurrences, with involvement of the chest wall, pleura and lung.

Carcinoma of the breast is a disease of major importance, and the foregoing account of other conditions is important only in so far as they may be confused with carcinoma, or as they may be implicated as precancerous conditions. It may be stated at the onset that a mass in the breast is carcinoma until it has been proved to be innocent. A few years ago we made a study of all the breast operations at the Pondville Hospital in a year, comparing the surgeon's preoperative diagnosis with the pathological report. The gross error in clinical diagnosis was 22 per cent. Others may be more alert or astute in diagnosis, but the fact will remain that there is a considerable margin of error in clinical appraisal of masses in the breast. Since it is axiomatic that early treatment is most likely to succeed in mammary carcinoma, it follows that it is better to "look and see" than to "wait and see," in dealing with a mass in the breast.

Not only is the diagnosis of carcinoma of the breast difficult, but there is also a wide margin of error in the diagnosis of the presence of axillary node metastasis. The diagnosis of the presence of supraclavicular metastasis or of remote dissemination, is equally subject to wide error. However, an attempt should be made to appraise the extent of the disease in order to plan rational therapy.

Little need be said in regard to signs and symptoms of mammary carcinoma. The presenting manifestation in nearly all cases is a mass, discovered accidentally by the patient. It is ironical that in a region that lends itself so readily to inspection and palpation, the tumor is often far advanced when first discovered. Rarely, a bloody discharge, axillary metastases, or remote manifestations are the first presenting

symptom. Adherence or puckering or dimpling of the skin, often elicited only by skilful and painstaking examination, is one of the surest diagnostic criteria, although even this finding is not pathognomonic. Skin involvement, ulceration, fixation to the pectoral fascia, skin nodules, and swelling of the arm are late manifestations; along with the evidences of diffuse dissemination.

The treatment of mammary carcinoma most promising for cure remains radical surgery. Several attempts have been made to establish radiation therapy as the equal or superior to surgery but in no instance has it been possible to show results as uniformly satisfactory as those achieved by surgery. Similarly, there have been reported series of attempted cure by simple mastectomy, or by a subradical procedure which preserves the pectoralis minor muscle; but these procedures cannot stand comparison with the results of radical mastectomy.

There has been a growing critical evaluation of criteria of operability, and an increasing awareness of the prognostic significance of some of the clinical characteristics of the tumor. The gravity of inflammatory carcinoma has long been recognized, and this condition is generally considered to be hopeless, and to contraindicate radical surgery. A few years ago we made a study of other clinical characteristics of the primary disease correlated with the prognosis, such as the size of the lesion, the degree and character of skin involvement, the extent of axillary involvement, the age of the patient, and similar presenting manifestations. Haagensen and Stout have recently offered a similar study in greater detail. Observers are in general agreement as to the graver prognosis in younger women, the extremely bad prognosis associated with pregnancy and lactation, and the lessened chance of cure associated with evidences of local or axillary extension and involvement. These conditions must be considered as relative rather than absolute contraindications to operation, and an occasional cure may result even when markedly adverse conditions apparently prevail. Thus the criteria of operability are relative rather than absolute; and indeed radical surgery may occasionally be employed for palliation in the face of absolute contraindications such as demonstrable remote metastases.

It is likely that part at least of the progressive improvement in the end results of radical operation are to be attributed to improved selection of cases suitable for operation. Other factors in improving end results are a more favorable group; in that patients as a result of educa-

TABLE I

RESULTS OF RADICAL SURGERY
CARCINOMA OF THE BREAST—MASSACHUSETTS GENERAL HOSPITAL

Period	*Percentage Cures*
1894-1904	19
1911-1914	27
1918-1920	30
1921-1923	35
1924-1926	41
1927-1929	43
1930-1932	45
1933-1935	51

tion seek and secure proper medical advice at an earlier date. There has also been a progressive improvement in operative technique, or at least a dissemination of proper technique so that it is more regularly employed by a greater group of surgeons.

End-result studies have been carried out at the Massachusetts General Hospital on the patients operated upon for carcinoma of the breast since 1894. Table I shows the results in terms of 5 year cures for various periods.

It is noteworthy that although preoperative and postoperative x-ray therapy was employed sporadically, at no time could this practice be demonstrated to improve the results; and the procedure has been abandoned, except when it has been necessary to leave obvious malignant disease behind after operation in a poorly selected case. It is also noteworthy that the operations are performed by a large number of surgeons, and in recent years in an increasing number of cases by the resident staff. The operation has uniformly been a radical operation, with removal of both pectoral muscles and the axillary contents. It has not been necessary to employ skin grafting to effect closure except in rare cases; and it does not seem necessary or desirable to develop parchment thin skin flaps as advocated by some writers. The efficacy of the local operation is attested by the fact that operative field recurrences were only 11 per cent in the most recently studied series. Postoperative deaths, due to cardiac complications, pneumonia, sepsis and pulmonary embolus, were 2 per cent in the same series of cases.

Certain factors of significance in the prognosis should be emphasized. When the disease is limited to the breast, 75 to 80 per cent of cases are five year cures. When the axilla is involved, the cures drop to 33 per cent. The grade of malignancy, based on criteria first formulated by Greenough, is of great importance. Carcinomas of higher grades of malignancy show a higher incidence of axillary metastasis and a lower curability than do lower grades of comparable extent. There is also a greater incidence of local recurrence in cases of higher grade of malignancy.

The prognosis is definitely better in the older age group, partly because the younger women exhibit cancers of higher grades of malignancy, as a rule. Small carcinomas offer a better prognosis than large carcinomas, and skin involvement is definitely a factor of increased gravity. In our most recent series a biopsy performed at the time of operation nearly doubled the likelihood of recurrence in the operative field. The extent of axillary involvement seems to be of great importance. While the cases without any involvement show a high degree of curability, those with a definite finding of only one or two metastatic nodes are nearly as favorable; and it is only in the group with multiple nodes involved that the poorer prognosis of node metastasis is manifested.

It is well recognized that freedom from evident recurrence for five years does not constitute an absolute cure, but this period does give an opportunity to appraise the results of treatment, and permits relatively early evaluation of trends in the results. It is also well to emphasize that there is still a large but fortunately diminishing group of patients who are inoperable when first seen. For the recurrent and primary inoperable cases it is necessary to resort to palliative measures. The most effective palliation of the local manifestations of disease consists in radiation therapy. The efficacy of artificial menopause in the younger women with recurrences has long been recognized. The results of this procedure are most marked in the patients with skeletal metastases. More recently the older age group has shown a promising response to the administration of estrogens, or of testosterone. While the mechanism of the improvements in these cases is obscure, there is reason to confide that great advances will be made in their use, and that increased understanding may shed light on the problem of carcinoma of the breast.

RECENT OBSERVATIONS ON THE DYNAMICS OF THE PULMONARY CIRCULATION*

A. COURNAND

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THE essential function performed by the pulmonary circulation is to transfer blood from the right to the left ventricle and thereby to bring it into intimate contact with alveolar air. Still another function has been assigned to the lesser circuit, namely the storage of blood in the pulmonary vessels. Blood stored in the lungs could be used as an emergency reserve to help fill the left ventricle when sudden increased demand in systemic blood flow is not paralleled by an increased venous return to the right heart and would, if need be, damp the effect of unequal discharge of both ventricles.

For many decades physiologists have tried to decide whether blood flow, pressures and volume variations in the pulmonary circulation are the expression of the passive position taken by this circuit in the general phenomena of the vascular system or whether they are affected by changes in pulmonary vascular resistance regulated by an active vasomotor system. I shall attempt in this presentation to discuss, in a limited way, our present day knowledge of this problem in the light of recent physiologic and physiopathologic evidence.

The two chief characteristics of the dynamics of the pulmonary circulation may best be stated as follows: (a) the blood flow through the lungs is identical to the blood flow through the entire systemic circulation, except for momentary differences, (b) the pressures in the right ventricle, pulmonary artery and capillaries are lower than in corresponding structures of the systemic circulation.

From these characteristics several facts may be deduced. First: the energy developed by the right ventricle in performing its mechanical work, i.e., stroke volume times mean pressure in the pulmonary artery,

* Under a grant from the Commonwealth Fund.
Read at the Stated Meeting of The New York Academy of Medicine, March 7, 1946.

is much less than that developed by the left ventricle. This explains the unequal muscular development of both ventricles.

Second: the small rise in pressure in the pulmonary artery during ejection is due to its greater distensibility in proportion to its capacity as compared to the aorta. Pressure-volume diagrams obtained with sections of both large vessels bear out this fact directly,[1] while measurement of pulse wave velocity[2] (3 meters per second in the pulmonary artery of the dog as compared to 4-5 meters in the aorta) confirms it indirectly.

Third: the resistance to flow in the pulmonary vessels is much less than in the systemic vessels, the mean pressure difference between the pulmonary artery and the left auricle being 1/5 of the mean pressure difference between the aorta and the right auricle. This low resistance is chiefly related to particular details of structures of the vessels: (a) the arterioles are few and their walls show very little smooth muscle, (b) the precapillaries are numerous and very large, sometimes larger than the arterioles, (c) the capillaries are short, with remarkable ability to increase their capacity by simple distention, (d) the veins are short and very distensible.

Fourth: the pulmonary circulation time must be short and the time of exposure of blood to alveolar air, likewise very short.

Blood pressures, blood volume, and circulation time in the pulmonary circulation of dog and normal man. One of the chief obstacles to accurate measurements of pressures in various parts of the pulmonary circulation of dogs lies in the difficulty of access to these parts and the abnormal physiologic conditions under which measurements have usually been obtained. Very recently, Hamilton, Woodbury and Vogt[3] have developed a method which permits the recording of pressures in the pulmonary artery and vein of unanesthetized, intact dogs, several weeks or months after their recovery from an operation during which the distal ends of special cannulae were placed in contact wtih the pulmonary vessels, while their proximal ends were sewn under the skin of the thoracic cage; these cannulae served later as a guide for the introduction into the vessels of needles connected to manometers. By this method pressures in the pulmonary artery of several dogs averaged 37/10 mm. Hg. with a mean pressure of 20 mm. Hg., while the average pulmonary vein pressure varied during one cardiac cycle between 12 and 2 mm. Hg. The pressure gradient between artery and vein, largest during early systole, reached practically zero at the end of diastole,

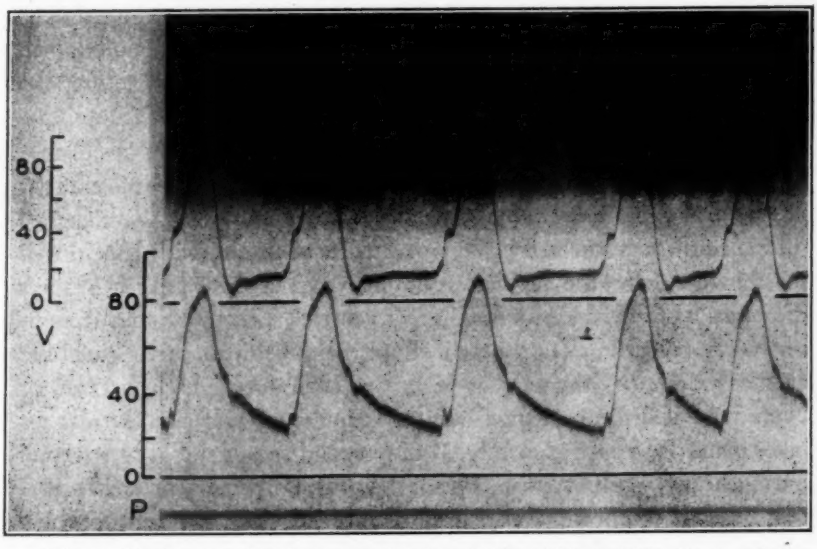

Fig. 1. Simultaneous blood pressure tracings in the right ventricle (top) and the pulmonary artery (bottom). *In this and the following records scales are in mm Hg. (For description of this and of the following figures see text.)*

another evidence of the small resistance to flow in the intervening arterioles and capillaries. In the course of many experiments they observed that pressure in the pulmonary artery rose with larger output from the right ventricle, while pressures in the pulmonary veins increased with some lag; but that a rise in pulmonary vein pressure closely followed increased resistance in the systemic circulation.

With Bloomfield, Lauson, Breed, and Richards[4] we have measured pressures in the right ventricle in 14 normal human subjects under metabolic conditions which were nearly basal, the blood flow in this group averaging 3.6 liters/min/m^2B.S. as compared to a standard figure of 3.1 liters. The ventricular systolic pressure averaged 25 mm. Hg. ranging from 18 to 30 mm. Hg., the pulse pressure, i.e., the difference between diastolic-filling pressure and peak of systolic pressure, ranged within the narrow limits of 21 to 27 mm. Hg.

Satisfactory records of pulmonary arterial pressures in man have, up to now, been difficult to obtain, on account of very marked superimposed oscillations due to motions of the catheter. In 4 normal individuals, where satisfactory tracings were recorded, the pressures averaged 25/8 mm. Hg. with a mean pressure of 15 mm. Hg. Fig. 1

illustrates an excellent record of simultaneous pressure tracings, in the right ventricle and pulmonary artery, obtained through a double lumen catheter in a patient in congestive heart failure where, therefore, the systolic and diastolic pressures were high.[5]

With a large blood flow and a low resistance, the mean circulation time is necessarily very rapid. After allowance is made with most methods used in experimental and clinical work, for transit of the chemical substance through the extra-pulmonary parts of its circuit, it is estimated that blood reaches the capillaries within 2 to 3 seconds after it has left the right ventricle, and reaches the left ventricle 2 seconds later. Roughton,[6] very recently, using a new method in normal man, investigated the capillary time, i.e., the average length of time during each circulatory cycle in which gas exchange between capillary blood and alveolar air takes place. It is, approximately, ¾ of a second at rest and ⅓ of a second during heavy work. Within this short interval a perfect or nearly perfect gaseous equilibrium, as is well established now, is reached, which speaks in favor of the high degree of efficiency attained by the pulmonary circulation in performing its essential respiratory function. Making apparently sound assumptions, Roughton went on to calculate the total area of the capillary walls and the total volume of capillary blood involved in this exchange—respectively 38 square meters and 60 cc. during rest. On the basis of the probably correct assumption that the capillary blood volume in the pulmonary vascular system constitutes, as in other regional vascular systems about 15 per cent of the entire volume, the circulating pulmonary blood volume under basal conditions would amount to 400 cc. or 8 per cent of the total circulating blood volume. This figure compares well with the value of approximately 10 per cent given by Kuno[7] who measured pulmonary blood volume directly on dogs in the heart-lung preparation.

A summary of standard measurements of blood flow, pressures, pulmonary blood volume in normal man under basal condition is given in Table I. Circulating pulmonary blood volume, and pressure, in the lesser circulation, are, however, not static as would appear from this Table. They are continuously influenced by the output of the right ventricle, the resistance in the pulmonary circuit and the effect of back pressures in the pulmonary veins resulting from variations in left ventricular output. We shall, therefore, consider the dynamic relationship between flow, pressure, and circulating blood volume in the lesser circulation

TABLE I

SOME MEASUREMENTS OF THE PULMONARY CIRCULATION IN NORMAL MAN, SUPINE AND UNDER BASAL CONDITION

Blood Flow	lit/min	5.5
	lit/min/m² BS	3.1
Pressures		
Right Ventricle		
Syst/Diast	mm Hg	25/2
Pulmonary Artery		
Syst/Diast	mm Hg	25/8
Mean	mm Hg	15
Capillary		
Mean	mm Hg	between 8—2 (appx.)
(Oncotic)	mm Hg	25
Blood Volume as a fraction of Total Blood Volume		1/10

under varying physiological conditions, such as changes in position and in intrathoracic pressure.

Increase and decrease in pulmonary blood volume, according to the experimental work of Drinker, Churchill and Ferry[8] are easily accommodated by the capacious vascular bed. The blood volume increases with larger discharge of the right ventricle and smaller discharges of the left and conversely decreases with smaller discharges of the right ventricle and larger of the left. Variations in the circulating blood volume within the lungs necessarily originate during the short periods in which, under normal physiological conditions, the two ventricular outputs differ. There is good evidence also brought out by the work of Hamilton and his co-workers,[9] using the dye technique, that under physiologic conditions in man, pulmonary blood volume variations are positively correlated with stroke volume variations.

Measurement of the vital capacity, within the limits of accuracy of this procedure, is also an excellent means of demonstrating qualitative changes in pulmonary blood volumes, since Drinker, Peabody and Blumgart[10] have shown that storage of blood in the lungs is at the expense of the air spaces. It is well known that vital capacity decreases in normal man as he moves from the standing or sitting to the recumbent position. In the latter position venous return from the abdomen and lower limbs

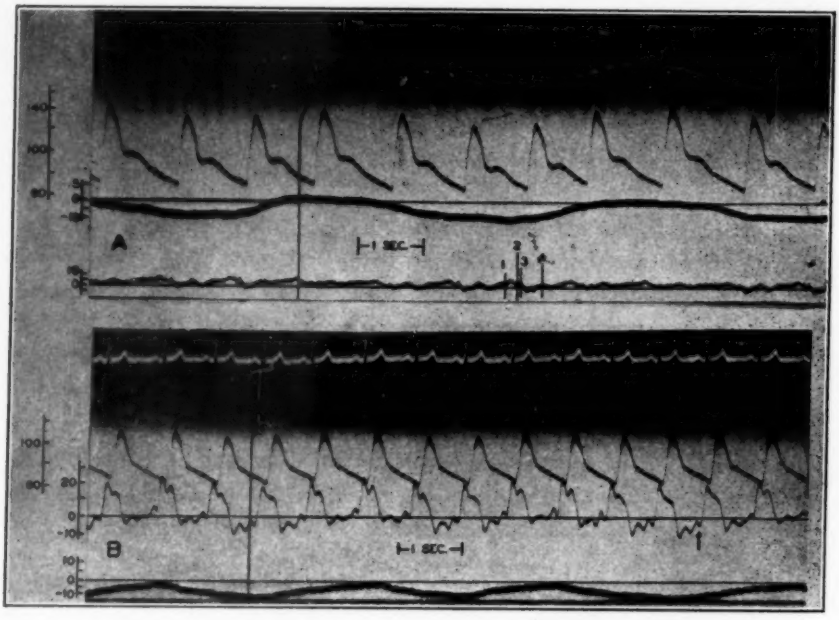

Fig. 2. Simultaneous blood pressure tracings in (a) femoral artery, pleura, and right auricle and in (b) femoral artery, right ventricle and pleura. Simultaneous electrocardiographic tracings at top of each record—vertical line indicates parallax between electrocardiogram and blood pressure tracings.

to the thorax is increased, the stroke volume of the right ventricle becomes larger, causing a rise in the pulmonary artery mean pressure and active congestion of the lungs. A convincing demonstration of the increase of the cardiac output in the recumbent position has been given by McMichael and Sharpey-Schafer[11] using the "Direct Fick" method. The importance of the increase of the venous return in the mechanism under discussion is stressed by the observations made in man by Hamilton and Morgan[12] and later by Dow,[13] which indicated that the decrease in vital capacity associated with a change to the recumbent position is lessened or prevented by the application of pressure cuffs on the four limbs.

Influence of various types of breathing upon blood pressure and blood flow in the pulmonary circulation. In the course of still unpublished studies of the effects of intrathoracic pressure variations upon the dynamics of the pulmonary circulation in man done in collaboration

with Lauson, Bloomfield, Breed and Richards,[14] and more recently with Motley, we have taken simultaneous pressure records in the right auricle and/or the right ventricle and the femoral artery, together with pneumographic tracings, during (a) quiet breathing, (b) deep breathing, (c) prolonged holding of breath in inspiration and expiration with opened or closed glottis and (d) intermittent pressure breathing. In a few cases with artificial pneumothorax, intrapleural pressures were recorded in addition. Examples of simultaneous pressure recording in the right auricle or ventricle, the femoral artery and the pleura in two cases of therapeutic pneumothorax during quiet breathing are shown in Fig. 2.

Interpretation of this and the following records in terms of blood flow variations stems directly from the extension to man, of Starling's law of the heart. If pressures in the right ventricle in successive cardiac cycles are measured exactly at the end of diastole and if the corresponding value of intrapleural pressure is subtracted from it, one obtains the effective diastolic (sometimes called net initial) pressure. This effective diastolic pressure is related to the degree of stretch of the filled ventricle. If the pulse pressure is then measured from the end of diastole to the peak of systole, the degree of response to the stretch and presumably the variations in stroke volume may be qualitatively estimated. An analysis of several hundred cardiac cycles of the tracings obtained in the patient illustrated in Fig. 2 (section B) during quiet and deep breathing has been made in this manner by Dr. Lauson, the result of which indicates a direct linear relationship between the effective diastolic pressure and the pulse pressure of the same beat. In most of our studies the pleural pressure is therefore unknown. However, the pulse pressure variations may be taken as indicating variations in stroke volume in the right heart and as the same argument applies to the left ventricle, variations in pulse pressure in the femoral artery may be interpreted as variations in left ventricular discharge, if in these short intervals the state of the peripheral vascular bed can be considered to be essentially unchanged. Since increase or decrease in peripheral vascular resistance would result respectively in an increase or a decrease in pulse pressure, blood flow remaining the same, this factor must also be taken into account in the interpretation of pulse pressure variation.

Using this method of analyzing tracings it would appear that in normal man during quiet breathing there is no evidence of unequal discharge of both ventricles. This confirms similar observations made by

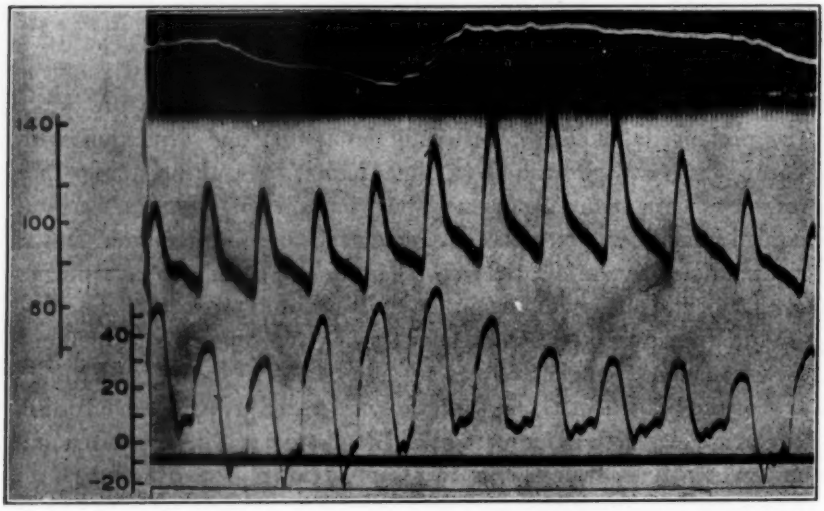

Fig. 3. Simultaneous pneumogram (top row), electrocardiogram (2nd row), blood pressure tracings in the femoral artery (3rd row) and in the right ventricle (bottom row) during deep breathing. Downward stroke of the pneumogram indicates inspiration —upward stroke—expiration.

Hamilton in animals.[15] However, during deep breathing, the evidence is in favor of unequal stroke volume of the two ventricles. In Fig. 3 it is seen that during deep inspiration the pulse pressure in the right ventricle is very large, while it is small in the femoral artery; whereas, the reverse occurs during expiration, when the pulse pressure increases markedly in the femoral artery and decreases in the right ventricle.

The following interpretation may then be given: (a) during inspiration the fall in intrathoracic pressure favors venous return, filling of the auricle and right ventricle. With the consequent rise in ventricular output, the pulmonary arterial mean pressure increases and blood is forced through new capillaries, as the distended lung tends to create an increased resistance in the capillaries already perfused. At the same time less blood is displaced from the actively congested lungs into the pulmonary veins than is being received into the lungs from the pulmonary artery. (b) When the respiratory cycle is reversed, relaxation of the lungs by displacement of blood causes an increase in pulmonary venous return, and left ventricular output, as evinced by a rise in the femoral artery pulse pressure. Meanwhile, the higher intrathoracic pressure

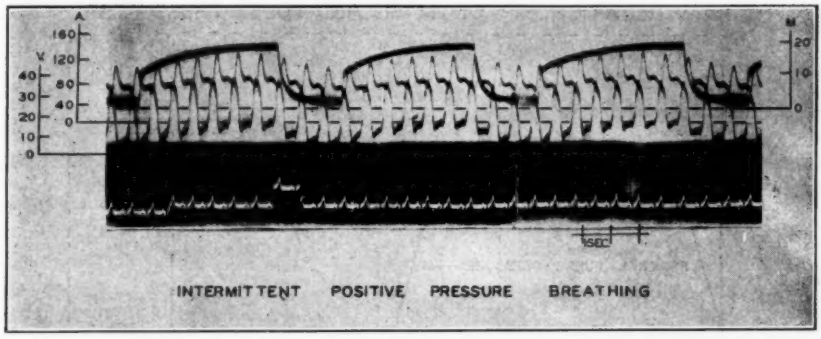

Fig. 4. Simultaneous tracings of mask pressure (M), and blood pressures in the femoral artery (A) and in the right ventricle (V) during intermittent pressure breathing.

decreases the venous return to the right auricle, causing a smaller discharge of the right ventricle.

The mechanism involved in intermittent pressure breathing with positive intrapulmonary pressure inflating the lung, followed by passive deflation, is exactly the reverse of the one just discussed in deep breathing. One typical example of intermittent pressure is illustrated in Fig. 4. The tracings were obtained in a normal young intern who volunteered for the study of a new type of artificial respiration apparatus. Inflation of the lungs under positive pressure and passive deflation were obtained through a special valve converting continuous positive pressure, supplied by a pressure tank, into an intermittent pressure transmitted through a mask to the lungs. It is easy to see the effect of the intrathoracic pressure increase and decrease upon the level of the pressure curves in the right ventricle and femoral artery. But only a beat to beat analysis of pulse pressure changes, in relation to the mask pressures, gives an idea of the magnitude of the probable unequal discharge of both ventricles. This relationship is illustrated in Fig. 5. It is seen that while pressure rises in the mask, the femoral pulse pressure becomes larger presumably as blood is forcibly displaced by the high intra-alveolar pressure into the pulmonary veins, thus increasing the left ventricular discharge. Meanwhile, the pulse pressure decreases in the right ventricle in spite of a marked increase in pulmonary vascular resistance; this points to a smaller discharge from the right ventricle, as the rising intrathoracic pressure causes a reduction of blood return from

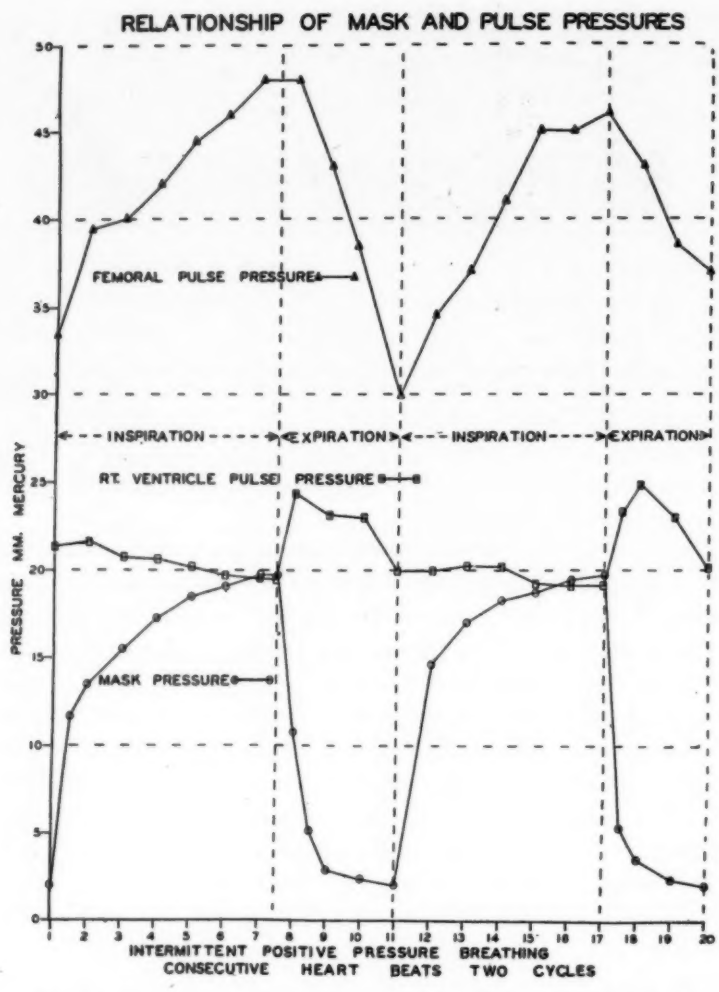

Fig. 5. Chart showing a beat to beat analysis of mask and pulse pressure changes illustrated in Fig. 4.

the large veins into the right auricle. During the short passive expiration the mask pressure falls rapidly, the lower intrathoracic pressure now favors venous return, hence, increased discharge of the right heart reflected in the marked pulse pressure rise. An increasing volume of blood is now held in the lung capillaries the capacity of which suddenly increases as the pressure in the alveoli drops. Therefore, the venous

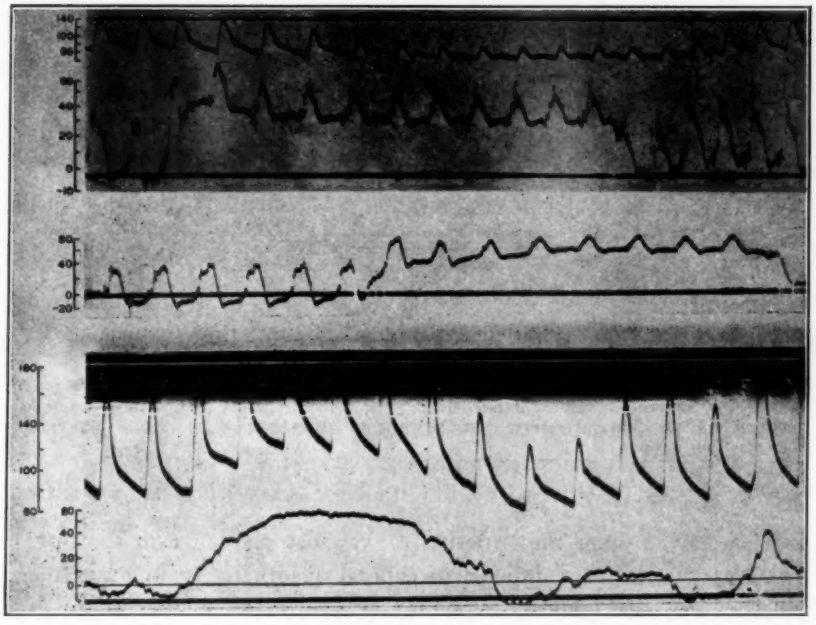

Fig. 6. Effects of a forced expiration upon blood pressure in (a) the right auricle and femoral artery (bottom row), (b) the right ventricle (middle row) and (c) the right ventricle and femoral artery (top row).

return to and the output of the left ventricle is lessened significantly as witnessed by the considerable reduction in the femoral artery pulse pressure.

The modus operandi of intrathoracic pressure variations upon flow, pressures and circulating volumes in the pulmonary circulation becomes clear from these studies: (a) changes in the general level of the pressure curves in the auricle, ventricle, pulmonary artery and veins, and even in the systemic large arteries are passive due to simple propagation of the intrathoracic pressure; (b) variations of the latter influence the venous return and, therefore, the discharge of the right ventricle; (c) finally, the state of distention or relaxation of the lung parenchyma in deep breathing and, in the case of intermittent pressure breathing, the variations of resistance to flow created by intra-alveolar pressure regulate the amount of blood stored, the size of the capillary bed perfused, and the return of blood to the large pulmonary veins. The effects of this pul-

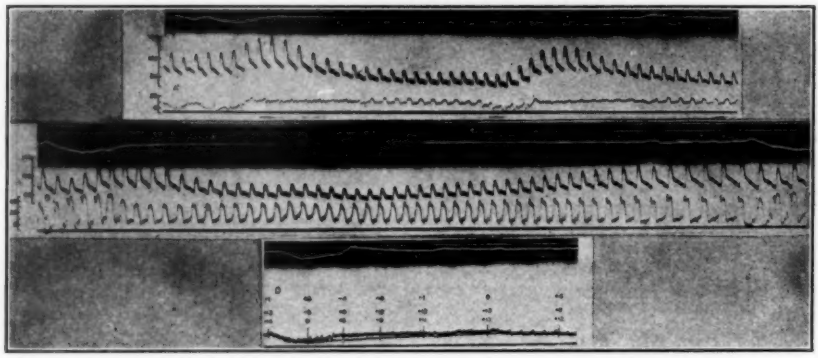

Fig. 7. Effects of a forced expiration maintained over a long interval of time upon the blood pressures in the right auricle and the femoral artery (top row), the right ventricle and the femoral artery (middle row) and the right auricle and a peripheral vein (bottom row).

monary factor upon the variation of vascular resistance in the intrapulmonary vessels are difficult to express quantitatively in man, since we lack the measurement of pulmonary vein pressure essential to determine the pressure gradient forcing blood through the vascular bed. Animal experiments carried out by Hamilton, Woodbury and Vogt[3] indicate, however, that intra-alveolar pressure variations are effective in temporarily creating marked variation in vascular resistance.

With this background I shall now present briefly the effects of a forced expiration upon right heart and femoral pressures. At the bottom of Fig. 6 are shown tracings of pressures in the right auricle and femoral artery, recorded during a forced expiration of short duration against a closed glottis. The intrathoracic pressure increased markedly as revealed by the auricular tracing and the diastolic pressure level of the femoral artery, but at the same time the femoral pulse pressure became larger indicating greater discharge of the left ventricle. In the next two rows, the effects of the same type of breathing upon the right ventricle discharge are well illustrated by the sharp drop in right ventricular pressure during forced expiration and its rapid rise as inspiration is resumed. The femoral tracing of the first row in addition shows a marked reduction in the diastolic pressure level, associated with a considerable reduction in pulse pressure, indicating that the persistent decrease in output of the right ventricle is followed rapidly by a reduction in dis-

charge of the left.

Some questions regarding the adaptation of the entire circulatory system to such an extreme type of breathing, maintained over a relatively long interval of time are partly answered in Fig. 7. In the top row of this figure, we observe the effects of a prolonged expiration, similar to those just described. In the second row, a ventricular pressure tracing was substituted for the auricular. At first, while the forced expiration progresses, the right as well as the left, ventricular discharge is reduced; this is reflected by the diminishing pulse pressures. After 20 to 24 beats, the pulse pressure rises again, first in the right ventricle, and then in the femoral artery. The mechanism of this secondary rise in right ventricular output is tentatively illustrated in the last row. Simultaneous tracings of pressures in a peripheral vein and in the right auricle were here recorded during the course of a similarly prolonged forced expiration. The figures for pressure in the peripheral vein, and in the auricle, and for the pressure gradient between both indicate that during the Valsalva experiment the pressure in the auricle is higher than in the peripheral vein for a period of time of approximately 13 seconds in this instance; then as blood accumulates in the vein, its pressure progressively rises and presumably the consequent increase in filling pressure initiates the larger discharge of the right ventricle mentioned previously.

Role of the pulmonary vaso-motor system in the regulation of flow and pressures. In our discussion, so far, the active role played by the blood flow and the passive one played by the vascular bed have been emphasized. The question comes up now whether the vaso-motor system plays a part in the regulation of peripheral vascular resistance of the lung vessels. Since anatomists[16] have demonstrated that there exists a dual nerve supply, sympathetic and parasympathetic, going to the muscular structures of the pulmonary vessels, it is in order to find out about its physiologic significance.

To the debate started in the last century and so thoroughly reviewed by Tigerstedt[17] and Wiggers,[18] Hamilton[15] has recently brought new evidence denying that any active role is played by the vaso-motor system in the regulation of blood flow through the lungs in dogs. To a critical analysis of the probable inadequacies of the methods previously used by the proponents of an active vaso-motor system, in particular Daly, [19, 20] he has added experimental evidence acquired with his new

method of pressure recording[3] wherein the pulmonary arterio-venous pressure gradient is measured directly in the unanesthetized intact animal. An analysis of the results of his experiment with drugs such as epinephrine, acetylcholine, amylnitrite, and histamine, led him to the following conclusion:[15] (a) that the changes in arterio-venous pressure gradients, when they were present could always be related to changes in blood flow and, therefore, were not necessarily associated with changes in resistance, (b) that the lack of direct effect of the drugs as they were first passed through the pulmonary arterioles was in striking contrast to their immediate action on the systemic arterioles. Extending his argument to the physiologic action of exercise, Hamilton compared the latter effects upon the dynamics of the pulmonary circulation to the effects of the systemic vaso-dilator drugs. According to his views, which confirm previous experimental data obtained by Dunn,[21] as soon as the vaso-dilatation of arterioles rapidly following the onset of exercise, has taken place, venous return and, therefore, pulmonary blood flow increases. However, the pressure in the pulmonary artery and the pressure gradient between pulmonary artery and vein rise very little: the resulting lower quotient of arterio-venous pressure gradient over blood flow then expresses a reduction in pulmonary vascular resistance created by the opening up of many new vascular channels and favoring a more rapid circulation time. A confirmation in man of this purposeful adaptation of the pulmonary circulation to a physiologically induced increase flow, lies in the figures given by Roughton,[6] in the work previously mentioned, of the much shorter capillary time, during heavy work than during rest.

However, to discuss, whether the vaso-motor system plays a significant role in the regulation of the pulmonary circulation in man, we have to resort to indirect evidence, since we lack the essential measurement of arterio-venous pressure gradient. As a first evidence we may use observations which we secured during a study of the treatment of shock in man using the pressor amine methedrine. In Fig. 8 are shown tracings of pressures in the femoral artery and in the right ventricle recorded prior to and at short intervals following the intravenous injection of this drug. In addition cardiac output measurements were made immediately before the first series of tracings and shortly after the last. One notes that the diastolic and the pulse pressure in the right ventricle rose hardly more than by a few millimeters of mercury for

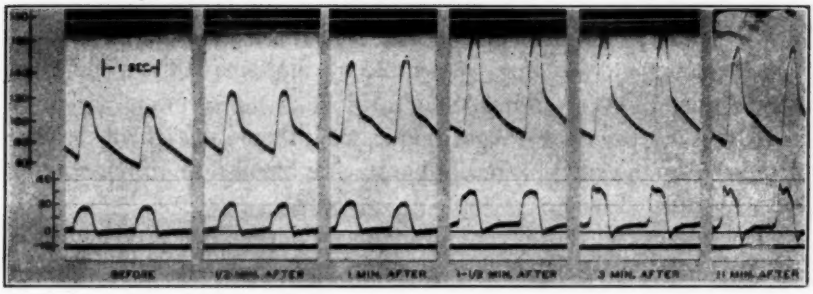

Fig. 8. Effects of the intravenous injection of the pressor amine, methedrine on the blood pressures in the femoral artery (top row) and in the right ventricle (bottom row).

the first 2½ minutes while the pulse pressure and systolic pressure in the femoral artery increased by more than 20 mm. Hg. This would seem to confirm the observations of Hamilton on the absence of direct action of the vaso-constrictive drugs on the pulmonary vessels. The later changes in the right ventricular pressure can probably be explained on the basis of (a) an increased blood flow which, 14 minutes after injection, was approximately 20 per cent larger than the control value, or (b) backflow pressure in the pulmonary vein as a result of increase resistance in the systemic circulation. [2, 22] The second evidence is supplied by some observations, made with Lauson and Bloomfield on right ventricular pressures and cardiac output measurements in 5 cases, with systemic arterial hypertension and good cardiac compensation, who were under the care of Dr. Goldring and Chasis. While the average mean pressure in the systemic circulation was elevated to 128 mm. Hg., the normal being about 95 mm. Hg., the average systolic and pulse pressures in the right ventricle were at the respectively normal figures of 25 mm. Hg. and 23 mm. Hg. Although definite conclusions should await further investigation, it seems reasonable to conclude from these limited data that the biological substance thought to cause increased resistance in the arterioles of the systemic circulation had in these cases no effect upon the arterioles of the lesser circulation. As a third type of evidence we shall have recourse to some observations of change in the arterial oxygen saturation made by Jacobaeus and Bruce,[23] after complete blocking of one main bronchus in normal young volunteers. The marked reduction, which persisted over relatively long periods of block-

ing, were of the order predicted with half of the mixed venous blood flowing through an unventilated area. Similar observations with nitrogen breathing by one lung were made by the same authors and confirmed since by Wright and Woodruff.[24] It would seem reasonable to think that if a vaso-motor regulation exists, it should in such an extreme case help shunt a physiologically purposeless blood flow to the contralateral ventilated lung.

Considering all this direct and indirect evidence, we may state that the demonstration of vaso-motor effects in the pulmonary circulation of man is still wanting. At best, it may be conceded that if any vaso-motor activity exists, under normal physiologic conditions, it is superseded by the much more potent mechanical factors regulating pulmonary blood flow. In contradistinction to the systemic circulation, where variations in peripheral resistance serve to regulate flow to various organs according to their needs, all parts of the pulmonary vascular bed and the alveolar spaces are equal in function, hence, there is little cause for a regulating mechanism of blood distribution under normal conditions.[15]

It remains to be decided whether the vaso-motor system could serve a useful purpose in regulating the amount of blood stored in the lungs. If it is correct, as I have attempted to show, that the variations in pulmonary circulating blood volume are dependent upon (a) the discharge of both ventricles, (b) the state of distension or retraction of the lung parenchyma, and (c) the intra-alveolar pressure, then vaso-motor regulation is not essential. In cases of emergency such as the early period of exercise, the sudden fall of systemic arterial pressure, caused by vaso-dilatation in the vascular bed of the muscles, may be prevented by an increased discharge of the left ventricle. The conditions favoring this purposeful increase in pulmonary venous return are thought to be (a) either a preliminary passive congestion of the lung, due to a strong epinephrine-like action on the systemic arterioles, with back pressure effects, during the pre-exercise period of excitation,[14] or else (b) a preliminary active congestion of the lungs, due to deep inspirations, the discharge of the left ventricle being then increased by a forceful expiration as exercise starts.[25]

If one agrees with Tiemann and Daiber,[26] that two types of blood channels exist in the lungs, one with active circulation, the other working as a lock, then vaso-motor regulation becomes indispensable. How-

ever, against the conception of lung blood depot, as postulated by Hochrein[25] on the basis of this description, there is, it would seem, lack of anatomic justification. As to the clinching physiologic evidence, which lies in the measurements of sequestrated blood, this is, for obvious reasons, still missing.

We shall now turn to the discussion of some observations made during the study of pathological conditions which have an important bearing on the problem of dynamics of the circulation in man.

Clinical investigation of the pulmonary circulation offers an immense field to test physiologic concepts, but methods of study have been until recently inadequate. We shall, here, limit ourselves to the discussion of some problems in which we have been interested:

Mechanism of blood shunting from one part of the lungs to another. Two methods, based on the measurement of respiratory gas exchange may be used in man, to study redistribution of blood, following pneumonia, atelectasis, collapse therapy or partial lung resection, namely (a) the determination in the arterial blood of the oxygen saturation and (b) the simultaneous but separate measurement of each lung's ventilation and gas exchange using the technique of bronchospirometry, which we owe to Jacobaeus, Frenckner and Björkman.[27]

Reduction in arterial oxygen saturation may be taken to indicate that blood circulates in areas of the lungs improperly or not ventilated. In the absence of a simultaneous measurement of the oxygen saturation of mixed venous blood, the degree of arterial oxygen unsaturation, gives only a qualitatively rough approximation of the proportion of blood circulating through unventilated lung areas. In pneumonia and atelectasis, measurements of the arterial oxygen saturation, show that the blood flow persists for some time in unventilated parts of the lungs. Blood is shunted away from these areas only after the pericapillary pressure, due to exudation, transudation and organization of tissue fluids has increased, diverting blood to other channels through better ventilated areas. As we have shown with H. Maier,[28] after lobectomy blood will continue to flow through the poorly ventilated remaining lobe and arterial oxygen saturation may remain low until the latter is again effectively ventilated. In artificial pneumothorax, the arterial oxygen saturation remains normal. According to Hamilton an increased resistance to flow is brought about by the homolateral rise in intrathoracic pressure, and blood flow is redistributed, preferably through the still

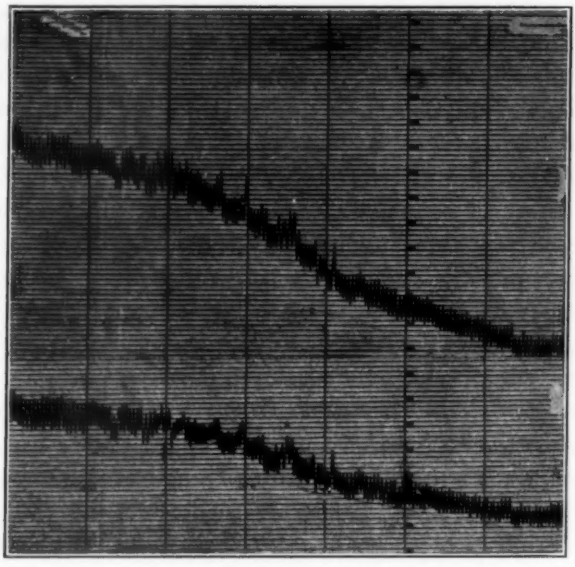

Fig. 9. Simultaneous tracings of ventilation and oxygen intake in each lung separately obtained by the bronchospirometric method. Inspiration upward, expiration downward, oxygen intake of each lung calculated from the slope—vertical lines of the curves at one minute interval—quiet breathing during the first two minutes, leg movements during the next 3 minutes, recovery during the last 2 minutes.

ventilated areas of the collapsed lung and the contralateral lung.

The bronchospirometric method permits a better qualitative estimate of this process of blood redistribution than the measurements of arterial oxygen saturation. The proportional share of each lung in the total oxygen consumption calculated from the slopes of the tracings (Fig. 9) may be taken as a measure of the relative blood flow through each lung, providing the breathing mixture is high in oxygen and the arterial oxygen saturation remains complete. If, in addition, the degree of saturation of the mixed venous blood were estimated directly or indirectly then the absolute values of separate flow could be calculated. In Table II, data on one case with artificial pneumothorax, and one case after lobectomy are presented to illustrate the method. It is seen that in these two patients at rest and during exercise the ventilation and the circulation on the right side were approximately reduced to the same extent.

Very extensive studies having now been carried out in all types of

TABLE II

VENTILATION AND CIRCULATION THROUGH THE RIGHT LUNG AT REST AND DURING EXERCISE IN (a) ONE CASE OF RIGHT ARTIFICIAL PNEUMOTHORAX AND (b) ONE CASE OF RIGHT LOWER LOBE LOBECTOMY

	Rest		*Mild Exercise*
	Normal	*Obsv.*	*Obsv.*
(a) Art. Pnx.			
Right Lung			
Ventilation % of total	55	45	45
Circulation % of total	55	41	45
(b) Lobectomy			
Right Lung			
Ventilation % of total	55	44	39
Circulation % of total	55	40	35

surgical disease of the lungs, of therapeutic collapse and pulmonary resection, the following conclusions concerning the problem of blood shunting are tentatively offered in support of the opinion of Hamilton stated above.

Redistribution of blood flow after partial lung collapse and resection depends upon local mechanical conditions. Among these stand out local ventilation, intrathoracic pressures, and local increase in peri-vascular tissue resistance by parenchymatous organization or by complications such as pleurisy and empyema. A small increase in resistance, in one lung, one lobe, or in lobules will cause the blood to be shunted away from the diseased into the intact lung.

Dynamic adaptation to the reduction or the absence of blood flow through one lung. Since it is assumed that the capacity of the pulmonary vascular bed is great, it would appear that its reduction by half and the routing of the entire blood flow through one lung should have little effect upon vascular resistance and, therefore, right intraventricular pressure.

In Table III are tabulated data in 14 subjects with little or no circulation through one lung which indicate that doubling the blood flow through one lung does not increase the intraventricular systolic pres-

TABLE III

RIGHT VENTRICULAR PRESSURES AND BLOOD FLOW IN 3 GROUPS OF PATIENTS (a) AFTER PNEUMONECTOMY (b) WITH FIBROTHORAX (c) WITH THERAPEUTIC PNEUMOTHORAX

Group	*No. of Cases*	*Right Ventricular Pressures*	*Blood Flow* lit/min/ m^2 BS
		Syst/Diast mm Hg	
(a) Post-Pneumonectomy	5	30/1	3.3
(b) Fibrothorax	4	27/—1	3.4
(c) Artificial Pneumothorax	5	24/0	4.6

sure. In 5 cases of pneumonectomy, three adults and two children, the average right ventricular pressure measured from 4 to 6 years after the lungs were resected, is, in all but one, at the upper limit of normal. In only one case, that of a man of 69 operated on six years previously for a carcinoma of the bronchus and who had then already a significant degree of bilateral emphysema, was there any evidence of pulmonary hypertension, the right ventricular systolic pressure being 36 mm. Hg. In the 4 other cases, the figures are well within the normal range.

In two children of this group studied with Lester and Riley,[29] we measured the maximum oxygen consumption during an exhausting type of exercise and compared them with similar figures in a control group of normal children of the same size and age. In the children with only one lung, the value of maximum oxygen intake, which is related to maximum cardiac output, was identical to the control value. These observations are offered as a further evidence that in subjects with one lung, who were not restrained in their physical activity since pneumonectomy, maximum pulmonary blood flow was not reduced and pulmonary hypertension did not develop after several years. In the four cases of fibrothorax and five of artificial pneumothorax, there was no evidence either of pulmonary vascular hypertension. In one of the cases of fibrothorax, restudied two years later, however, a moderate pulmonary hypertension had developed. The figures are specially significant in the group with artificial pneumothorax, where as a result of the multiplicity of measurement, the figures indicate that the subjects

were not nearly under basal conditions as shown by the increased blood flow. In spite of this increased blood flow, the ventricular systolic and pulse pressure remained within normal range.

Preservation of normal pressure-flow relationship in patients with only one normally functioning lung may be achieved in two ways which complement each other: (a) an increase in the number of capillaries which are perfused in the remaining lung, (b) an increase in the diameter of the lung capillaries which according to Poiseuille's law could be very small.

Effect of direct communication between the systemic and the lesser circulation. There is another type of pathological condition where a consistent increase in blood flow through the pulmonary circulation may not be associated with pulmonary hypertension, namely the direct shunt of blood from the aorta to the pulmonary artery through a patent ductus arteriosus.

The technique of right heart catheterization lends itself to a physiologic, rational diagnosis of some forms of congenital heart disease. By the use of pressure recordings in and blood sampling from both branches of the pulmonary artery, the right ventricle, and auricle, congenital defects may be recognized in terms of volume of blood shunted and the effects of the abnormal communication upon pressures may be evaluated. Drs. Dexter and Burwell who have made brilliant use of the resources of the technique of catheterization have already studied six cases of patent ductus arteriosus with surgical confirmation and reported to me recently that in all these cases the pulmonary arterial mean pressure was normal, even though in one individual they estimated the shunt through the ductus to be 8 liters per minute.

We have, however, very recently studied in collaboration with Dr. Janet Baldwin, a young girl of three years of age, with a flow of approximately 5 liters through a patent ductus arteriosus, compared to a systemic flow of 2 liters. A marked degree of hypertension in the pulmonary artery had already developed, the pulmonary artery systolic and diastolic pressures being 55/39 with a mean pressure of 46 mm. Hg. or approximately 3 times normal.

There is no doubt that extension of studies of this type will prove of great value not only in the diagnosis but in the comprehension of the physio-pathology of congenital heart defects.

Influence of chronic pulmonary disease upon the development of

TABLE IV

RIGHT VENTRICULAR PRESSURES, PULMONARY BLOOD FLOW AND LUNG VOLUME MEASUREMENTS IN 17 CASES OF CHRONIC PULMONARY EMPHYSEMA AND FIBROSIS WITHOUT CARDIAC ENLARGEMENT

Group	*No. of Cases*	*Right Ventric. Pressures*	*Blood Flow* lit/min/	*Hct.* %	*Residual Air / Total Lung Vol.* *Pred.*	*Obsv.*
		Syst/Diast mm Hg	m^2 BS		lit.	lit.
A. Emphysema without pulmonary hypertension....	4	24/1	3.0	41	1.3 / 5.3	2.9 / 5.9
B. Emphysema with pulmonary hypertension	4	44/4	3.1	47	1.2 / 5.0	3.6 / 5.6
C. Diffuse fibrosis	9	45/3	3.6	48	1.4 / 5.5	2.2 / 4.2

pulmonary hypertension. The presentation of this problem alone would justify a long discussion. Our concern here is to indicate that an investigative method is available which may help (a) to express somewhat quantitatively the degree of right ventricular strain in chronic pulmonary emphysema and/or fibrosis at a time when radiologic and electrocardiographic data are still equivocal or of no clinical value, (b) to identify the various factors which in these diseases may favor the development of pulmonary hypertension.

In Table IV we have summarized some studies made in collaboration with Drs. Bloomfield, Lauson, Breed and Richards.[4] We have correlated right ventricular pressure, pulmonary blood flow, hematocrit and lung volume measurements in 17 cases without clinical evidence of cardiac enlargement. The first and second groups comprise cases of chronic pulmonary emphysema without and with pulmonary hypertension, the third, cases of chronic pulmonary fibrosis complicated with emphysema. The data are remarkable in showing (a) that pulmonary hypertension had not developed in cases with moderate degree of emphysema, (b) but that in the group with the most marked degree of emphysema, hypertension in the lesser circulation was present, and finally, (c) that in the group with fibrosis and moderate emphysema and apparently small heart, pulmonary hypertension was already quite marked. For a

time, it was our impression that polycythemia played a decisive role in the early development of pulmonary hypertension, by increasing the resistance to flow. However, a breaking down of the hematocrit figures in the two groups of emphysema with and without hypertension, does not at present seem to lend support to this hypothesis.

Many factors are responsible for the increased resistance to flow in pulmonary emphysema and fibrosis. With adequate physiologic methods it should be possible to correlate some of the data as we have attempted in this limited series. In the future it will be of interest to the clinician that figures of pressures in the right ventricle and pulmonary artery be correlated with signs usually interpreted as indicating pulmonary hypertension and with studies of electrocardiograms, using the most recent methods for the detection of early right ventricular strain.

In this presentation, I have omitted discussing many problems of interest to the clinician. However, I shall have fulfilled my purpose if I provided adequate support to the following conclusions:

(1) The volume of blood contained in the pulmonary vessels is governed by the relative discharge of the two sides of the heart which are under the control of the dynamic changes in the systemic circulation.

(2) The capacity and the flexibility of the small vessels in the lungs are such that a several fold increase in blood flow may be accommodated with negligible pressure changes, a remarkable example of purposeful adaptation to function.

(3) Under variable physiologic conditions a clear cut demonstration of vaso-motor activity in the pulmonary vascular bed is still lacking.

(4) Sound physiologic methods for the study of the pulmonary circulation are now at the disposal of the clinical investigator and may be used for diagnostic purposes in well chosen cases of congenital cardiac malformation.

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CURARE AND INTENSIVE PHYSICAL THERAPY IN THE TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS*

NICHOLAS S. RANSOHOFF

INTRODUCTION

A METHOD of treatment of acute anterior poliomyelitis has been developed at the Monmouth Memorial Hospital in Long Branch, New Jersey, which utilizes the relaxing effect of curare and intensive physical therapy from the onset of the disease. Every attempt is made to reëstablish and maintain normal muscle physiology. In as much as any loss of normal muscle length is accompanied by loss of muscle strength, the full physiological power of the muscle is sought and developed.

Twenty-nine patients were treated in 1945 and, at the present time, there are twenty-one patients who are completely well. There are three patients who have paresis of one or more muscle groups. There are four patients who have paralysis of either a major muscle or an extremity. There are no residual abdominal or back muscle weaknesses. There was a single fatality due, in part, to the mechanical failure of the respirator.

Electromyography: Electromyographic studies were performed on all the patients admitted to the hospital with acute anterior poliomyelitis. The following observations were made:

1. There are resting action currents present in the muscles of patients with acute anterior poliomyelitis.

2. The resting action currents are diminished or obliterated by means of curare and intensive physical therapy in the form of stretching beyond the point of pain.

3. Sherrington's law of reciprocal innervation is interfered with in patients with acute anterior poliomyelitis, so that the antagonists may be more active than the agonists.

4. The administration of curare assists in the reëstablishment of the physiological phenomenon, reciprocal innervation.

* Presented before the Section of Orthopedic Surgery of The New York Academy of Medicine, November 15, 1946.

5. On voluntary contraction, a poliomyelitic muscle varies from the relatively normal in both potential and frequency.

6. The pathological stretch reflex is present in patients with acute anterior poliomyelitis. This is decreased or eliminated by the administration of curare.

Dosage: The dosage of curare which is used is 0.9 unit per kilogram of body weight every eight hours for the first twenty-four hours. This is always administered after meals. The preparation of curare which is used is Intocostrin (Squibb). It is administered by intramuscular injection. After the first twenty-four hours, the dosage is increased to 1.5 units per kilogram of body weight if there has been no adverse reaction. Over five thousand injections of Intocostrin have been given in 1945 and 1946 to patients with acute anterior poliomyelitis. Physostigmine, the pharmacological antidote for curare, has been administered only once and, whether or not that was necessary, is still a moot question. The policy has been established at the hospital that if there is doubt in anyone's mind, the physostigmine, which is always ready, is given.

Therapeutic Effects: The following therapeutic effects have been obtained:

1. Blurring of vision or diplopia. These are the symptoms indicative of adequate dosage.

2. Relief of pain.

3. Sufficient relaxation of muscles which have been in spasm to allow intensive stretching procedures.

4. Temporary exaggeration of muscle weaknesses present, enabling early discernment of minor weaknesses undetectable before curarization.

Physical Therapy and Occupational Therapy: The physical therapy procedures which have been adopted are designed to reëstablish normal, or as near normal, muscle physiology as possible. It is freely admitted that there can be no possible effect of the method of treatment on spinal cord pathology. It is maintained that the best possible results will be obtained with whatever muscle power can be salvaged by the following procedures in conjunction with the administration of curare.

Curare without physical therapy or physical therapy without curare will not give the desired results. This cannot be emphasized too forcibly. Muscle lengths are maintained by intelligent stretching. This stretching must be carried beyond the point of pain. It is best done by carrying the part to the point of pain and then, with gentle pumping movements,

increase the range of motion. Then rest and repeat. With each repetition, a greater range of motion will be obtained. Care and patience are imperative in these manipulations.

Exercises are designed primarily to develop and improve coördination and flexibility. That the muscles are strengthened through these exercises is coincidental. It is not implied that individual muscle group exercises are never given. They are. But the majority of the exercises are so designed that the part as a whole is the point of focus rather than an individual muscle.

Occupational therapy plays an important part in this regimen of treatment.

Psychological Approach: The confidence and coöperation of the patients must be obtained by the physical and occupational therapists. Every possible device must be used to keep the patients' morale at a high level. Certain standards of behavior in treating patients with acute anterior poliomyelitis have been established at the Monmouth Memorial Hospital. These are, in brief, as follows:

1. Never lie to a patient. If the patient is going to be hurt, tell him so.

2. Never bribe a patient in an endeavor to get his coöperation.

3. Make it a practice to spend some time in recreation with the patients daily. This may consist of roughhouse, reading, or innumerable methods of having the patients do things under the guise of play. This is essential so that the physical therapist does not become an ogre, but maintains a normal personal relationship with the patient. This is just as important for the adults as for the children. It is a *real* program based on elementary psychological principles.

Summary

1. A method of treatment of acute anterior poliomyelitis has been presented which utilizes the relaxing effect of curare to enable the immediate institution of intensive physical therapy, thus reëstablishing and maintaining normal muscle physiology.

2. Electromyographic studies were made on each of the twenty-nine patients with acute anterior poliomyelitis treated by the described method in 1945.

3. The dosage of curare recommended is 0.9 unit per kilogram of body weight every eight hours for the first twenty-four hours. It is then

increased to 1.5 units per kilogram of body weight if there has been no adverse reaction.

4. The physical and occupational therapy procedures which are used are based on the objective of reëstablishing and maintaining normal muscle lengths. Patients are made ambulatory as soon as possible, thus preventing loss of the kinesthetic sense of the upright position.

5. The psychological approach of the physical and occupational therapists to the patients is considered to be of great importance.

Conclusions

1. It is believed that the described method of treatment of patients with acute anterior poliomyelitis will accomplish the following: (a) Shorten the period of hospitalization. (b) Decrease the number of personnel necessary to care for the patients. (c) Give better functional results.

2. No claim is made that this is a cure for acute anterior poliomyelitis but that it is a better method of treatment.

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